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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,708	01/14/2004	Derek O' Hagan	PP-19768.002	3852

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,708	O' HAGAN ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28, 32-39, 42-48, 52, 54-64, 69, 72-101* is/are pending in the application.

4a) Of the above claim(s) *4,7,11,14,19-22,24,25,58-60,62,72-75,84 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1-3,5,6,8-10,12,13,15-18,23,26-28,32-39,42-48,52,54-57,61,63,64,69,76-83 and 86-101.

DETAILED ACTION

1. Claims 29-31, 40, 41, 49-51, 53, 65-68, 70, and 71 have been cancelled.

Claims 4, 7, 11, 14, 19-22, 24, 25, 58-60, 62, 72-75, 84, and 85 have been withdrawn.

Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26-28, 32-39, 42-48, 52, 54-57, 61, 63, 64, 69, 76-83, and 86-101 are under examination.

Response to Arguments

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude"

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26-28, 32-39, 42-48, 52, 54, 55, 61, 69, 76-83, and 90-101 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5-19, 24-26, and 35-40 of U.S. Patent No. 6,884,435. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to **(i)** microparticles comprising a biodegradable polymer, a cationic lipid, and a first polynucleotide-containing species adsorbed on the surface of the microparticles, wherein the first polynucleotide species constitute at least 5% of the total weight of the microparticles, the cationic surfactant is cetyltrimethylammonium bromide (CTAB), the biodegradable polymer is poly(lactide-co-glycolide) (PLG), the first polynucleotide-containing species encodes for an antigen derived from a pathogenic organism such as HIV, the microparticles further comprise an immunological adjuvant such as CpG ; the microparticles can contain 01-10 wt% cationic surfactant or additional microparticles comprising entrapped or adsorbed immunological adjuvants (claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26-28, 34-37, 43, 69, 76-79, and 90, 91, and 96-100), **(ii)** a method of producing the microparticles by obtaining a w/o/w emulsion comprising the polymer and the surfactant, removing the organic solvent from the solution and adsorbing the first polynucleotide-containing species to the microparticles (claims 52, 54, 55, 92-95, and 101), **(iii)** a method of delivering a therapeutic amount of polynucleotide to a host animal (claim 38), and **(iv)** a method of stimulating an immune response, wherein the immune response comprises a CTL immune response (claims 39, 42, 44-48).

The patent claims recite **(i)** a microparticle comprising a polymer such as PLG, a cationic detergent such as CTAB, and an antigen comprising a polynucleotide such as plasmid (example 7 discloses that the plasmid is pCMV) adsorbed on the surface of the microparticle, wherein the polynucleotide encodes for an antigen derived from a pathogenic organism such as HIV and wherein the microparticle is formed in the presence of the detergent and then exposed to the polynucleotide (the specification defines that a w/o/w solvent evaporation system can be used to form the microparticles, see column 13, lines 10-39); the microparticles further comprise CpG as an immunological adjuvant (claims 1, 5-13, 16, 17, 19, 20, 24-26, 35-37) and **(ii)** a method for raising an immune response by administering the microparticles to a vertebrate animal (the specification discloses that the intent of delivery is to use the particle as a vaccine to elicit an immune response in a vertebrate and to treat a disease, see column 4, lines 3-30; additionally the specification defines that a vertebrate can be a human, column 8, lines 45-52) (claims 38-40). The specification discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the microparticle (column 14, lines 6-10) and that the microparticles comprise 0.1 to 10% or 0.5 to 2 % cationic surfactant (column 13, lines 30-37). The specification also discloses that the cationic surfactant is not removed after the formation of the microparticles (column 13, lines 10-39). With respect to the limitation of the adjuvant being adsorbed on the surface of the microparticle, the specification discloses that adjuvants can be used to enhance the immunogenicity of the microparticles and that the adjuvants can be adsorbed on the microparticles (column 14, lines 36-51). With respect to the limitation

recited in claim 3, the specification discloses that the microparticles have a diameter of about 200 nm to about 30 μm that includes the range recited by claim 3 (column 5, lines 1-10). With respect to the limitation of the polynucleotide constituting 10-20% of the total microparticle weight (the instant claims 27, 28, 91, and 93), it would have been obvious to one of skill in the art to adjust the amount of delivered polynucleotide according to particular needs by varying the amount of adsorbed polynucleotide. It is routine in the art to vary the relative ratios of the microparticle components and test for the combinations that result in better activity.

Thus, the patent claims and the instant claim are obvious variants.

Applicant traversed the instant rejection on the grounds that the recitation of "*wherein the adsorbed first polynucleotide- containing species constitutes at least 5 percent of the total weight of the microparticles, wherein the cationic surfactant is present during formation of the microparticles, and wherein no cationic surfactant removal step is conducted subsequent to formation of the microparticles*" is neither taught nor suggested by the claims of US 6,884,435.

Citing MPEP 804, Applicant had previously noted that, when considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the patent specification can be used as a dictionary to learn the meaning of a term in the patent claim, but that the disclosure of the patent may not be used as prior art for purposes of an obviousness-type double patenting rejection. The Examiner had previously responded, urging that the patent

specification was used to define the microparticle characteristics in order to determine whether the claimed invention is an obvious variation of the invention claimed O'Hagan and further urging that the Examiner used only those portions of the specification pertaining to the invention claimed in the patent. As authority, the Examiner has provided the following citation from MPEP 804 II B, which pertains to In re Vogel, 422 F.2d 438,441-42, 164 USPQ 619, 622 (CCPA 1970) in which it was held that a certain portion of a the patent specification may be "considered" for an purposes of an obviousness-type double patenting analysis:

> Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel .... The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

In this regard, the Vogel Court more fully explained its reasoning as follows:

> The second analysis question is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? In considering the question, the patent disclosure may not be used as prior art. In re Boylan, supra [392 F.2d 1017, 55 CCPA 1041 (1968)]; In re Aldrich, 398 F.2d 855, 55 CCPA 1431 (1968). This does not mean that the disclosure may not be used at all. As pointed out above, in certain instances it may be used as a dictionary to learn the meaning of terms in a claim. It may also be used as required to answer the second analysis question above. We recognize that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim. A claim is a group of words defining only the boundary of the patent monopoly. It may not describe any physical thing and indeed may encompass physical things not yet dreamed of. How can it be obvious or not obvious to modify a legal boundary? The disclosure, however, sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether that thing has been modified in an obvious manner. It must be noted that this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the

> patent as a reference under 35 U.S.C. § 103, since only the disclosure of the invention claimed in the patent may be examined.

Thus, the Court in Vogel, examined a "tangible embodiment" within the claim. The Court specifically refused, on the other hand, to consider generic portions of the specification:

> ...We must now determine how much of the patent disclosure pertains to the invention claimed in the patent, which is a process to be performed with pork, to which all the patent claims are limited. The specification begins with certain broad assertions about meat sausages. These assertions do not support the patent claims. The patent claims recite "pork" and "pork" does not read on "meat." To consider these broad assertions would be using the patent as prior art, which it is not ....

The present case is analogous. The O'Hagan patent claims recite an adsorbed "antigen comprising a polynucleotide" whereas column 14, lines 6-10 of the specification pointed out by the Examiner pertains to adsorbed "macromolecules". Just as "pork" does not read on "meat" (which is held in Vogel to include pork), an "antigen comprising a polynucleotide" does not read on a "macromolecule". To consider the broad assertions regarding macromolecules in O'Hagan would be to improperly use O'Hagan as prior art. Similarly, the O'Hagan patent claims recite a "cationic detergent" whereas column 14, lines 6-10 of the specification pointed out by the Examiner pertains to "detergent". As above, to consider the broad assertions regarding detergents in the specification would be to improperly use the O'Hagan patent as prior art.

The Examiner has responded in the Office Action of December 23, 2008 by alleging as follows. (1) The disclosure in the '435 patent on which the Examiner relied in making the obviousness-type double patenting rejection is not a generic portion with which the specification begins and where the specification makes broad assertions about macromolecules and detergents. (2) The teachings of the macromolecule constituting 5% of the total weight of the microparticle and of the microparticles as

comprising 0.1 to 10% or 0.5 to 2% detergent specifically define the microparticles recited in the patent, which microparticles constitute a tangible embodiment. (3) The patent specification defines that the macromolecule could be a polynucleotide and that the detergent could be a cationic detergent such as CTAB (column 5, lines 28-35 and 65-67) and therefore, the teachings of the macromolecule constituting 5% (column 14, lines 6-1 0) and of the microparticles comprising 0.1 to 10% or 0.5 to 2% detergent (column 13, lines 30-37) do pertain to polynucleotides and cationic detergents such as CTAB.

Applicant argues that, while the assertions about macromolecules and detergents referred to by the Examiner may not be positioned at the beginning of the specification, this is hardly a rational basis for distinguishing In re Vogel. Moreover, rather than constituting a "tangible embodiment" as urged by the Examiner, the teachings referred to are generic, pertaining to a macromolecule (as opposed to a polynucleotide) and a detergent (as opposed to a cationic detergent). The fact that the patent specification elsewhere states that the macromolecule could be a polynucleotide and that the detergent could be a cationic detergent such as CTAB as argued by the Examiner is perfectly analogous to In re Vogel, wherein the patent specification stated elsewhere that the meat could be pork. Thus, as "pork" does not read on "meat" in Vogel, a "polynucleotide" does not read on a "macromolecule", nor does a "cationic detergent" read on a "detergent". To consider the broad assertions regarding macromolecules and the broad assertions regarding detergents would therefore constitute using the O'Hagan patent as prior art.

During the interview of April 7, 2009, the Examiner clarified that it was her belief that the instant case is not analogous to Vogel, because Vogel's description contained teachings pertaining to the genus (meat) but not the species (pork). (O'Hagan's description, on the other hand, contains teachings pertaining to both genus (macromolecule, detergent) and species (polynucleotide, cationic detergent).) The description of the patent in Vogel (US 3,124,462), however, pertains not only to meat products (see, e.g., col. 1, lines 24-69) but also to pork (see, e.g., col. 2, line 3 to col. 4, line 18). Accordingly, Vogel is on point, and O'Hagan's generic teachings in the specification pertaining to macromolecules may not be considered for purposes of an obviousness-type double patenting analysis based on the patent claims, which are directed to polynucleotides. Similarly, O'Hagan's generic teachings in the specification pertaining to detergents may not be considered for purposes of an obviousness-type double patenting analysis based on the patent claims, which are directed to cationic detergents. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Applicant's arguments are not new and were previously addressed. The present case is not analogous to Vogel. As opposed to Vogel, the teachings in the specification of O'Hagan et al. support the patent claims. Vogel only generally makes broad assertion about meat at the beginning of the specification and does not define that the meat could be pork. For these reasons, "pork does not read on meat". In contrast, the

teachings of macromolecules in O'Hagan et al. are not at the beginning of specification and are not general. O'Hagan et al. clearly defines that the macromolecule could be a polynucleotide (column 5, lines 65-67). Therefore, a polynucleotide reads on a macromolecule and all the teachings related to macromolecules pertain to polynucleotides. Similar considerations apply to CTAB.

For these reasons, Applicant's arguments are not found persuasive.

4. Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26, 28, 32-37, 54, 55, 61, 69, 76-83, and 90-101 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 11, 30, 31, 36, 37, 40, 43, 45-47, 58, 59, 71, and 79 of the U.S. Application No. 11/113,861. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to **(i)** microparticles comprising a biodegradable polymer, a cationic lipid, and a first polynucleotide-containing species adsorbed on the surface of the microparticles, wherein the first polynucleotide species constitute at least 5% of the total weight of the microparticles, the cationic surfactant is cetyltrimethylammonium bromide (CTAB), the biodegradable polymer is poly(lactide-co-glycolide) (PLG), the first polynucleotide-containing species encodes for an antigen derived from a pathogenic organism such as HIV, the microparticles further comprise an

adsorbed immunological adjuvant such as CpG and can contain 01-10wt% cationic surfactant (claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26, 29, 30, 34-37, 69, 76-79, 86, and 90, 91, and 96-100), **(ii)** a method of producing the microparticles by obtaining a w/o/w emulsion comprising the polymer and the surfactant, removing the organic solvent from the solution and adsorbing the first polynucleotide-containing species to the microparticles (claims 52, 54, 55, 92-95, and 101), **(iii)** a method of delivering a therapeutic amount of polynucleotide to a host animal (claim 38), and **(iv)** a method of stimulating an immune response, wherein the immune response comprises a CTL immune response (claims 39, 42, 44-48).

The application claims recite a microparticle comprising a biodegradable polymer such as PLG, a cationic detergent, an immunological adjuvant and an antigen derived from a pathogenic organism such as HIV, wherein both the immunological adjuvant and the antigen are adsorbed on the surface of the microparticle, wherein the biodegradable polymer is PLG, and wherein the microparticles are formulated into an injectable pharmaceutical composition (claims 1-5, 11, 30, 31, 40, 43, 45-47,58, 59, 70, and 71); the adjuvant comprises CpGs (claims 36 and 37). The specification discloses that the antigen can be a plasmid such as pCMV encoding gp120 and that the cationic surfactant can be CTAB (p. 1, paragraph 0002, p. 4-5, paragraph 0019, p. 7, paragraph 0037, p. 17, paragraph 0070, Example 7). With respect to the limitation of the size of the particles being between 200 nm and 20 μm, the specification discloses that the microparticles can have a diameter of 200 nm to 30μm. The specification also discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the

microparticle (p. 8, column 1, paragraph 0091) and that the microparticles comprise 0.1-10% or 0.5-2 % or cationic surfactant, wherein microparticle can comprise 1% detergent relative to the biodegradable polymer, and that the microparticles are obtained without removal of the detergent after particle formation (p. 18-19, paragraph 0075).

Thus, the application claims 1-5, 11, 30, 31, 36, 37, 40, 43, 45-4758, 59, 79, and 71 anticipate claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26, 28, 34-37, 52, 54, 55, 61, 69, 76-79, 86, and 90-101 of the instant application. Since the US Application No. 11/113,861 claims 1-5, 8, 10, 11, 13, 15-21, 24-27, 30, and 31 embrace all limitation of the instant claims, the patent claims and the instant claim are obvious variants of one another.

Applicant traversed the instant rejection on the grounds that the copending application has not issued as a patent and the claims may be amended/cancelled in the future. Applicant argues that, at a future time, the provisional double patenting rejection may be the only rejection remaining in the present application, in which case the rejection will be withdrawn in accordance with the provisions of MPEP 804. The Examiner has responded by arguing that what may happen in the future is irrelevant. However, what may happen in the future is not irrelevant, because it is possible that Applicant might needlessly reduce the scope of its claims by prematurely addressing the provisional rejection. Furthermore, Serial No. 11/113,861 is a continuation of Serial No. 09/581,772, which matured as O'Hagan above. Thus the arguments set forth above

in connection with the double patenting rejection over O'Hagan are analogous to the present provisional double patenting rejection as well.

Applicant's arguments are acknowledged; however, these arguments are not new and were previously addressed . Regardless of what may happen in the future, the rejection is maintained for the reasons set forth in the prior Office actions.

35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26-28, 32-39, 42-48, 52, 54-57, 61, 63, 64, 69, 76-83, 86-89, and 90-101 remain rejected under 35 U.S.C. 102(e) as being anticipated by O'Hagan et al. (U.S. Patent No. 6,884,435, of record), as evidenced by Thalhamer et al. (Endocrine Regulations, 2001, 35: 143-166).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

O'Hagan et al. teach a microparticle comprising a biodegradable polymer such as PLG, a cationic surfactant such as CTAB, and a polynucleotide adsorbed on the surface of the microparticle (claims 1-3, 5, 6, 90, and 100), wherein the microparticles have a diameter of 200 nm to 30 μm, wherein the polynucleotide constitutes at least 5% or 10% of the total weight of the microparticle, wherein the polynucleotide is a plasmid such as pCMV (i.e., comprising CpGs) and wherein the plasmid encodes an antigen derived from a pathogenic organism such as HIV gp120 (claims 1, 8-10, 12, 13, 15-18, 27, 28, 61, 69, 90, 91, and 100); the microparticle is formed in the presence of the cationic surfactant and the cationic surfactant is not removed after the formation of the microparticle and contains at least 5% (claim 1) (Abstract, column 2, lines 37-67, column 3, lines 17-34, column 5, lines 1-5, 28-35, and 65-67, column 9, lines 5-15, column 11, lines 1-6, column 12, lines 6-19, column 14, lines 1-12, Examples 2 and 7). O'Hagan et al. teach that the microparticles can be formulated into an injectable pharmaceutical composition, wherein the pharmaceutical composition further comprises an adjuvant such as an aluminum salt and wherein the adjuvant is adsorbed on the microparticle (claims 23, 26, 34-37, 55, 76-79) (column 14, lines 36-67, column 15, lines 66 and 67). O'Hagan et al. also teach a method of producing the above microparticle by forming a w/o/w emulsion comprising the cationic surfactant and the biodegradable polymer at a weight to weight ratio of 0.01:1, followed by the removal of the organic solvent and the absorption of the polynucleotide (claims 52, 54, and 92-95) (column 13,

lines 10-39). In addition to the above, O'Hagan et al. teach a method for raising an immune response by administering their microparticles to a human (claims 38, 39, and 45-48), wherein the immune response comprises a CTL response (claims 42 and 44) (column 4, lines 3-30, column 7, lines 25-35, column 8, lines 45-52). With respect to claims 27, 28, 91, and 93, O'Hagan et al. teach that the polynucleotide can constitute 0.1% to 10% of the total weight of the microparticle (column 14, lines 8 and 9); the value of 10% is the same as the claimed lower point of the claimed range, and therefore, O'Hagan et al. anticipate the range 10% to 20% or 10% to 30% recited in claims 27, 28, 91, and 93. With respect to the limitation of the microparticle comprising 0.1 to 10 wt% cationic surfactant (claim 96), O'Hagan et al. teach a weight to weight ratio of cationic surfactant to polymer of 0.001:1, i.e., the microparticle comprises 0.1% cationic surfactant (column 13, lines 30-37). With respect to the limitation of the microparticles comprising 0.5 to 2 % cationic surfactant (claims 97 and 101), O'Hagan et al. teach a weight to weight ratio of cationic surfactant to polymer of 0.005 to 1, i.e., the microparticle comprises 0.5% cationic surfactant (column 13, lines 30-37). With respect to the limitations recited in claims 98 and 99, O'Hagan et al. teach a ratio of cationic surfactant to biodegradable polymer of 0.01:1, i.e., the amount of surfactant is 1% relative to the biodegradable polymer (column 13, lines 30-37). With respect to the limitation recited in claims 56, 63, 64, and 86, O'Hagan et al. teach that the microparticle composition can comprise additional microparticles with the adjuvant adsorbed on their surface (column 14, lines 35-51); with respect to the limitation of the microparticles further comprising an immunological adjuvant (claim 64), it is noted that the

microparticles of O'Hagan et al. comprising adsorbed plasmid contain CpGs, i.e., they further contain an immunological adjuvant. With respect to the limitations recited in claim 57, O'Hagan et al. teach that the microparticle composition can comprise additional microparticles with entrapped adjuvant (column 14, lines 35-51). With respect to the limitation of microparticle eliciting a Th1 response (claim 43), it is noted that this is an inherent property of CpGs (see Thalhamer et al., p. 145, column 2); since the microparticles of O'Hagan et al. comprise CpGs, they must necessarily induce a Th1 immune response.

Since O'Hagan et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

Applicant traversed the instant rejection on the grounds that no specific examples falling within the claimed range are disclosed by O'Hagan. Example 7 of O'Hagan describes pCMVgp120 DNA loads ranging from 0.84 to 2.36% with decreasing loading efficiencies ranging from 88% to 59%. These do not meet the at least 5% loadings claimed in claim 1 (broadest claim). In an attempt to address this point, the Examiner had previously urged that "the loading efficiency is not 100% and therefore, in order to achieve a loading of 5%, one would have to use more than 5% input polynucleotide." However, this is not at all clear, as loading efficiency was seen to decrease with increasing target load. Moreover, the present rejection is an anticipation rejection and thus pertains to what was actually done in O'Hagan, rather than what might or might not have been obvious in view of O'Hagan.

At column 14, lines 8-9, O'Hagan teaches that "macromolecules are added to the microparticles to yield microparticles with adsorbed macromolecules having a weight to weight ratio of from about 0.0001 : 1 to 0.25:1 macromolecules to microparticles, preferably, 0.001 : 1 to 0.1, more preferably 0.01 to 0.05." See col. 14, lines 6-10. As an initial observation, it is noted that this particular teaching is directed to macromolecules, rather than polynucelotides as claimed. The Examiner has argued that O'Hagan clearly defines that the macromolecule can be a polynucleotide (column 5, lines 65-67) and therefore, the disclosed ranges apply to polynucleotides. In support the Examiner urges that "the MPEP states that A REFERENCE THAT CLEARLY NAMES THE CLAIMED SPECIES ANTICIPATES THE CLAIM NO MATTER HOW MANY OTHER SPECIES ARE NAMED".

O'Hagan, however, has not clearly named the species in question, at least by the standards required for anticipation. In this regard, see In re Arkley, 455 F.2d 586, 587-88, 172 U.S.P.Q. 524, 526 (CCPA 1972) (A "reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing and combining various disclosures ...")

To arrive at the presently claimed invention, one of ordinary skill in the art would have to choose polynucleotide-containing species from among the numerous other macromolecules disclosed in O'Hagan. This choice would have to be based on teachings found in different portions O'Hagan. Thus, the claimed composition cannot be said to correspond to a "species" named by O'Hagan.

Moreover, assuming that the ranges of O'Hagan are applied in their entirety to the entire range of species embraced by the term "macromolecules," the ranges described are not sufficiently specific to constitute anticipation under the statute and the case law. In this regard, the standard for anticipation is high:

> When the prior art discloses a range which touches *>or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, >and the reference teaches a broad range, ** depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. **>See, e.g., Atofina v. Great Lakes Chem. Corp, 441 F.3d 991,999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points. "Id. at 1000, 78 USPQ2d at 1424...

The facts of the present case are analogous to those above, if not more favorable to Applicant. As indicated above, no specific examples falling within the claimed range are disclosed by O'Hagan (Example 7 of O'Hagan describes pCMVgpl20 DNA loads ranging from 0.84 to 2.36%). With regard to the macromolecule ranges described in O'Hagan, the narrow range disclosed in O'Hagan discloses microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.01 : 1 to 0.05:1 (i.e., ranging from 0.01 : 1 or 0.01/[1+0.01]=0.99 percent up to 0.05:1 or 0.05/[1+0.05]=4.76 percent). There is thus no overlap between the ranges of instant claims (in claim 1, the broadest claim pending, the polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles).

The intermediate range disclosed by O'Hagan involves microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.001:1 to 0.1:1 (i.e., ranging from (0.001:1 or 0.001/[1+0.001]=0.1 percent up to 0.1:1 or 0.1/[1+0.1]=9.1 percent). Thus, the intermediate range (0.1 to 9.1 percent) overlaps the numerical range of claim 1 (polynucleotide- containing species constitutes at least 5 percent of the total weight of the microparticles), but not claim 27 (polynucleotide-containing species constitutes 10 to 30 percent of the total weight of the microparticles) or claims 28, 91 and 93 (polynucleotide-containing species constitutes 10 to 20 percent of the total weight of the microparticles).

The broad range disclosed by O'Hagan involves microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.0001:1 to 0.25:1 (i.e., ranging from (0.0001:1 or 0.0001/[1+0.0001]=0.01 percent up to 0.25:1 or 0.25/[1+0.25]=20 percent). Thus, the broad range (0.01 to 20 percent) overlaps the numerical range of claim 1 (polynucleotide- containing species constitutes at least 5 percent of the total weight of the microparticles), overlaps the numerical range of claim 27 (polynucleotide-containing species constitutes 10 to 30 percent of the total weight of the microparticles) and embraces the numerical range of claims 28, 91 and 93 (polynucleotide-containing species constitutes 10 to 20 percent of the total weight of the microparticles).
For the intermediate range, however, the high "macromolecule" concentration is nearly two orders of magnitude (91 times) higher than the low macromolecule concentration. For the broad range, the high "macromolecule" concentration is more than three orders of magnitude (2500 times) higher than the low macromolecule concentration.

In this regard, it was held by the Federal Circuit in Atofina, supra, that a much narrower disclosure of 100-500 degrees C by a prior art reference did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. This was true even though the claimed range was completely embraced by the wide range taught in the reference. Moreover, the disclosure of an even narrower range of 150-350 degrees C by the prior art reference was not sufficient for anticipation of the claimed range of 330-450 degrees C in Atofina, even though the disclosed 350 degree endpoint of the narrower range was embraced by the claimed range.

Moreover, whereas the prior art and claimed ranges in Atofina were based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison, if you will (i.e., macromolecule vs. polynucleotide- containing species).

In the Office Action of December 23, 2008, the Examiner responds as follows: "While Applicant is right in pointing out that the values of 0.01 : 1 to 0.05:1 are not the same as the claimed 5% and 10% values, O'Hagan also teaches a polynucleotide to microparticle ratio of 0.25:1 (see column 14, lines 1-10), i.e., the polynucleotide constitutes 20% of the total weight of the microparticles. Since MPEP states that patents are relevant art for all they contain, by teaching that the polynucleotide constitutes 20% of the total weight of the microparticles, O'Hagan anticipates the values of at least 5% (claim 1), 10 to 30% (claim 27), and 10 to 20% (claims 28, 91, and 93)." However, even assuming for the sake of argument that the O'Hagan specification had happened to explicitly teach microparticles with adsorbed polynucleotide (rather than

macromolecule) having a weight to weight ratio of from 0.0001 : 1 to 0.25:1 polynucleotide to microparticles (i.e., 0.01 to 20 percent polynucleotide), it remains the case that the Examiner is erroneously treating the 20 percent value as if it were specific example. It is not. Rather, it is the endpoint of a range.

As noted in Atofina supra "the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." For this reason, the disclosed ranges of 150-350 degrees C and 100-500 degrees C were held not to anticipate the claimed range of 330-450 degrees C in Atofina. As in Atofina, in the present case, an allegedly disclosed range of 0.01 to 20 percent polynucleotide does not anticipate a claimed range of 5 percent or more (claim 1), a claimed range of 10 to 20 percent (claims 28, 91 and 93) or a claimed range of 10 to 30 percent (claim 27). The Examiner further states the following at pages 10-11 of the Office Action of December 23,208: "Applicant argues that Atofina makes clear that the endpoint of a range is not a specific example. This argument is not found persuasive because in Atofina the claimed range was 330-450°C without specifically reciting the value of 350°C which is the endpoint value of the range of 150-350°C disclosed by the art. In the instant case, the claims specifically recite the endpoint of 20% and O'Hagan specifically discloses a range having the endpoint value of 20%; therefore, O'Hagan anticipates the claimed 20% (or at least 5%) value."

In the Examiner interview of April 7, 2009, the Examiner recognized that the 0.25:1 value was an endpoint of a range. The Examiner urged, however, that the present fact pattern was distinguishable from Atofina, because in Atofina, the endpoints

of the claimed range (330-450 degrees C) didn't not correspond to any of the endpoints in the reference (100-500 degrees C, more preferably, 150-350 degrees C), whereas in the present application, an endpoint of one of the ranges claimed (i.e., 20 percent in claims 28, 91, 93) did correspond to an endpoint in the reference.

In rebuttal, several points should be made. First, the MPEP clearly indicates that the "sufficient specificity" test of Atofina is applicable to situations where the prior art discloses a range which "touches ... the claimed range". See MPEP 2131.03 II (emphasis added). Consequently, the holding in Atofina that "the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points" applies to the instant case. The Examiner, on the other hand, is clearly treating the endpoint as if it were a specific example in spite of the holding in Atofina: "the claims specifically recite the endpoint of 20% and O'Hagan specifically discloses a range having the endpoint value of 20%; therefore, O'Hagan anticipates the claimed 20% (or at least 5%) value."

In essence, the Examiner is attempting to distinguish the fact pattern in Atofina by urging that the present fact pattern, in which the endpoint disclosed in O'Hagan is" the same as the endpoint of certain claimed ranges, is somehow more compelling than the fact pattern in Atofina, wherein the endpoint disclosed in the prior art fell squarely within the claimed range. In fact, the present fact pattern is more favorable to the Applicant.

In Atofina, a disclosed endpoint fell squarely within a claimed range, yet did not anticipate the claimed range. To argue that the court in Atofina would have, on the

other hand, found anticipation had the disclosed endpoint merely touched the claimed endpoint is not logical. In other words, the argument that if the claimed range had been 350-450 degrees C in Atofina, rather than 330-450 degrees C (a narrower claimed range), the claimed range would have been anticipated by the disclosed range of 150-350 degrees C, simply because the endpoints matched, is a non sequitur. Yet that is, in essence, what the Examiner appears to be saying when she urges that because the claims specifically recite an endpoint of 20% and because O'Hagan specifically discloses an endpoint value of 20%, O'Hagan anticipates the claimed 20% value. Again, the Examiner's position arises from the Examiner focusing on the fact that O'Hagan describes microparticles with adsorbed macromolecules having a weight to weight ratio of 0.25:1, while ignoring the fact that this ratio is set forth in O'Hagan as an endpoint of a range rather than an independent value, thereby ignoring the holding in Atofina.

With respect to cationic detergent, the reasons for why O'Hagan falls short of being an anticipatory reference are analogous to those set forth above in conjunction with the claimed polynucleotide-containing species. Claim 52 sets forth a process in which a w/o/w emulsion is formed that comprises polymer and cationic surfactant, wherein the weight-to-weight surfactant-to-polymer ratio is in the range of from 0.0025:1 to about 0.05:1.

O'Hagan teaches that "a weight to weight detergent to polymer ratio in the range of from about 0.00001:1 to about 0.1:1 will be used, more preferably from about 0.0001:1 to about 0.01:1, more preferably from about 0.001:1 to about 0.01:1, and even

more preferably from about 0.005:1 to about 0.01:1." See col. 13, lines 32-37. Note that this passage pertains generally to "detergents," which are defined at col. 5, lines 28-36 to "include surfactants and emulsion stabilizers. Anionic detergents include, but are not limited to, SDS, SLS, sulphated fatty alcohols, and the like. Cationic detergents include, but are not limited to, cetrimide (CTAB), benzalkonium chloride, DDA (dimethyl dioctodecyl ammonium bromide), DOTAP, and the like. Nonionic detergents include, but are not limited to, sorbitan esters, polysorbates, polyoxyethylated glycol monoethers, polyoxyethylated alkyl phenols, poloxamers, and the like."

To the extent that these ranges embrace the ranges of method claim 52, they are not sufficiently specific to constitute anticipation under the statute and the case law. See Atofina supra. As above, it should be reemphasized that whereas the prior art and claimed ranges in Atofina were based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison (i.e., detergents vs. cationic detergent).

With regard to the specific examples in O'Hagan, in Example 2 of O'Hagan, 12.5 ml of a 4% PLG solution (which contains 0.5 g PLG) and a 50 ml of a 0.5% CTAB solution (which contains 0.25 g CTAB) are employed, corresponding to 50% CTAB relative to PLG, or a weight-to-weight surfactant-to-polymer ratio of 0.5:1. These percentages are much greater that the range of cationic surfactant used in claim 52. See also Example 1 of the present specification, wherein 16.6 ml of a 6 % PLG solution (which contains 1 g PLG) and a solution containing 10 mg CTAB are employed,

corresponding to a mere 1% CTAB relative to PLGA repeat procedure employed a mere 4% CTAB relative to PLG.

Note also that the 50% CTAB relative to PLG used in producing the microparticles of O'Hagan is outside even the broadest weight to weight detergent to polymer ratio range described in O'Hagan (i.e., a range of from about 0.00001:1 to about 0.1:1). It is recognized, however, that the microparticles produced by O'Hagan using 50% CTAB relative to PLG are washed with water by centrifugation four times, which would have reduced the CTAB content. As indicated in Singh et al., Proc. Natl. Acad. Sci. USA, 2000, 97:811-816 (of record) at page 815, right column, third paragraph, washing twice with water by centrifugation results in a CTAB level of 4 micrograms of CTAB per milligram of PLG polymer, or a CTAB concentration of 0.4% relative to PLG. The amount of CTAB in the microparticles of Example 2 of O'Hagan, which were washed four times (rather than two) would be at least as low, given that the same relative amount of CTAB was used to form the microparticles of O'Hagan as was used in Singh.

Unlike O'Hagan, the microparticles in claims 1 and 52 are not washed to remove cationic surfactant subsequent to microparticle formation. This is also true of the microparticles of Examples 1 and 2 in the present specification--consequently, the same amount of detergent used to form the microparticles (1% and 4% CTAB relative to PLG) is also present in the microparticles to which the DNA was adsorbed.

Moreover, in O'Hagan, even though 50% CTAB relative to PLG was used in producing the microparticles, the amount of detergent in the microparticles to which the

DNA is adsorbed is far less, specifically, not more than 0.4% CTAB relative to PLG, for the reasons discussed above. This amount is less than the amount of cationic detergent in claims 97-99 and 101.

Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Applicant's arguments are not new and were previously addressed. As indicated in the no-final Office action mailed on 12/23/2008, the instant case is not similar to *Atofina*. The argument that O'Hagan et al. disclose the 20% value as an endpoint and not as an independent value is not found persuasive. O'Hagan et al. do not have to teach this value as an independent value. O'Hagan et al. specifically disclose 20%. Regardless of how it is disclosed (i.e., as an endpoint of a range or as an independent value), 20% is disclosed and anticipates the limitation of "at least 5%" in claim 1. Applicant argues that the Examples in O'Hagan et al. do not disclose the claimed values. This is not found persuasive because O'Hagan et al. disclose these values. Patents are relevant for all they contain (see MPEP 2123 [R-5]).

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633